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# Clinical Management of Atopic Dermatitis

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## 1. Introduction

Atopic Dermatitis (AD) is a common inflammatory, pruritic skin disorder. It is a chronic disease with often relapse. Several factors including genetic predisposition, allergies to specific foods, irritant chemicals, and aeroallergens are thought to be the cause of AD. Diagnosis is difficult, and often occurs after ruling out other disorders with a clinical presentation resembling atopic dermatitis.

## 2. Definition

Atopic Dermatitis is a chronic relapsing inflammatory condition of the skin that occurs most frequently in childhood and may spontaneously resolve or continue throughout a person's life span leading to lifelong sensitivity to irritants and allergens (Habif, 2008). It occurs as a result of several interrelated factors including genetic, immunologic and environmental issues, which ultimately cause a disruption in the epidermal barrier function leading to the development of dry, pruritic skin. The itching can be severe lasting throughout the day and worsening at night, which can lead to sleep disruptions and dramatically reduce the patients' quality of life (Bieber, 2008). Episodes of AD can be triggered by events such as psychological stress, exposure to irritants and allergens or as a result of seasonal or climate changes (Habif, 2008). Additionally, patients with AD are at an increased risk of developing infections especially due to *Staphylococcus Aureus* and Herpes Simplex Virus, asthma and allergic rhinitis (Bieber, 2008).

## 3. Epidemiology

Over the past several decades' industrialized nations have seen a dramatic rise in the incidence of AD (Ghazvini, et al. 2010). This disease occurs primarily in childhood affecting 15-30% of children and 2-10% of adults. It most frequently begins in early childhood with 45% of cases occurring within the first six months of life and 85% of cases diagnosed within the first five years (Bieber, 2008).

## 4. Pathophysiology

The pathophysiological mechanism of AD is multifactorial involving genetic, structural and immunological elements. The hallmark characteristic of AD is epidermal barrier dysfunction.

In normal individuals there are three factors that contribute to intact epidermal barrier function; structural proteins, lipids and proteases. Alterations in these components contribute to epidermal barrier dysfunction in AD patients. Additionally, genetic dysfunctions can be classified into two distinct groups; mutations occurring in genes encoding for epithelial structures and mutations occurring in genes encoding for elements of the immune system (Bieber, 2008). Lastly, immunological dysfunction appears to play a critical role in the pathogenesis of AD and involves alterations in T-cells, B-cells, eosinophils and IgE production.

#### **4.1 Structural factors**

There are several factors that lead to epidermal barrier dysfunction including changes in the stratum corneum, decreases in lipid levels and loss of function of a crucial protein called filaggrin. This is compounded by alterations in the expression of enzymes, such as peptidases within the epidermal layer leading to further breakdown of this protective barrier. Ultimately, the disruption of the epidermal barrier facilitates the penetration of environmental allergens and promotes allergic skin inflammation (Bieber 2008; Caubet & Eigenmann 2010).

#### **4.2 Genetic factors**

Researchers have identified several candidate genes that contribute to both the structural and immunological dysfunctions seen in AD. There is a genetically determined dominance of Th<sub>2</sub> cells, which produce cytokines including Interleukin-4 (IL-4), Interleukin-5 (IL-5) and Interleukin-13 (IL-13). These cytokines play a role in the synthesis of IgE, which is upregulated in 85% of patients with AD. Additionally, there is a loss of function mutation in the gene encoding for the protein filaggrin, which is a crucial protein in cutaneous barrier function (Bieber 2008; Caubet & Eigenmann, 2010).

#### **4.3 Immunological factors**

The immunological factors that contribute to AD are multifactorial and complex. As stated previously, disruptions in the epidermal barrier facilitate the penetration of allergens. These allergens are presented to the Langerhans Cells (LCs) located within the epidermal layer, which migrate to the lymphoid organs where they present the allergen to the Th<sub>2</sub> cells. (Callard & Harper 2007) Additionally, activated dendritic cells serve to stimulate memory Th<sub>2</sub> cells and migrate to the lymph nodes where they further increase the systemic pool of Th<sub>2</sub> cells by stimulating naïve T-cells. This increase in circulating T-cells results in the development of skin lesions through the production of inflammatory cytokines IL-4, IL-13, IL-5 and IL-12. Further promotion of the inflammatory response is modulated by Th<sub>2</sub> cells through the upregulation of adhesion molecules on endothelial cells and increases in high affinity receptors for IgE on LCs and other antigen presenting cells. Lastly, eosinophils appear to play a role through secretion of cytolytic proteins resulting in further damage to the epithelial cells (Caubet & Eigenmann 2010).

Other immunological factors that contribute to the pathogenesis of the disease include a down regulation of toll-like receptors (TLRs) within the epidermal cells. These TLRs serve to bind bacterial, fungal and viral structures leading to the activation of epithelial cells to produce antimicrobial peptides. These receptors are down regulated in the presence of IL-4, IL-13 and IL-10 in patients with AD. The result is patients are at an increased risk of developing skin infections and are often colonized with *Staphylococcus Aureus* (Bieber, 2008).

## 5. Clinical presentation

The clinical appearance of AD varies with disease severity. At all stages, patients have dry skin. Intensely pruritic, erythematous papules associated with exudates are seen in the acute phase of AD in infants. In the infantile stage (0-2 years old), the distribution of the rash is normally located on the face, chin, cheeks, scalp, trunk and extensor surfaces, but not on the nose or the diaper area (Deshazo, 2009). As the disease becomes more chronic, there is associated lichenification and the distribution of the rash is mostly seen on the wrists, ankles and neck in the childhood stage (2 years old-puberty) (Deshazo, 2009; Lipozencic, 2010). Approximately, 40% of childhood AD persists into adulthood (Bettrani, 2007). The distribution of rash in adults is similar to the childhood form mostly noticeable on the upper arms, back, wrists, dorsa of hands, fingers, feet and toes (Deshazo, 2009). The presence of pustules within areas of dermatitis suggests a secondary infection. Lesions with a less distinct distribution should prompt a search for an alternative diagnosis.

## 6. Diagnosis

The diagnosis of atopic dermatitis is based on a constellation of clinical signs and symptoms, physical examination and history. Laboratory tests are unnecessary and skin biopsy has been found to be little value, but they can exclude other diagnosis in adults. Although the majority of AD patients have elevated total serum IgE, up to 30% of these patients have normal total serum IgE and show no allergic sensitization to food or aeroallergens (Schmid-Grendelmeier, et al. 2005). However, monitoring of IgE remains a nonspecific finding of AD.

Normally, diagnosis is confirmed by chronicity of symptoms, pruritis, and age-specific morphology and distribution of symptoms (Ong P, et al. 2008). However, well-defined criteria are important in the diagnosis of AD and diagnostic criteria developed by Hanifin and Rajka are widely accepted (see Table 1). The American Academy of Dermatology has also developed diagnostic criteria for AD (Leung & Hong, 2007). Please see Table 2.

There are many exacerbating factors that are triggers, which can expedite the progress of inflammation. These triggers are found in food allergens, bacteria, viruses, stress and opportunistic pathogens. One of the major triggers is the microorganism *Staphylococcus Aureus* due to the fact that is organism secretes a toxin which can stimulate action of T cells (Ghazvini, et al. 2010). Among viruses, herpes simplex virus has been identified as one of the possible triggers of AD (Ghazvini, et al. 2010). Diagnostic testing is mainly utilized to determine specific allergens that may be causing the condition. These tests include:

- Allergy or skin prick test – a positive prick test indicates the presence of IgE antibodies specific for a certain antigen. However, the positive predictive value is only 50%, which means a patient who has a positive test should undergo confirmatory testing through food challenges (Ghazvini, et al. 2010).
- Atopy patch test- an atopy patch test (APT) is currently used to evaluate allergen without comparison with another accurate and reliable method, because no gold standard exists for aeroallergen provocation in AD. The APT is presumed to reflect delayed-phase clinical reactions. The patch test is performed by applying a patch consisting of large test chambers containing allergens. The patch is applied to the back for 48-72 hours on areas that are affected by AD or have not been treated with topical creams or ointments (Akdis, et al. 2006; Lipozencic, 2010).

- Food challenge – This is the most accurate test to diagnose allergy to food; skin reactions are expected to present up to 24 hours after testing. There are three patterns of skin reactions which can be observed with this test:
  - Immediate type reactions such as urticaria, erythema and angioedema may occur without worsening the AD symptoms and they may occur within a few minutes after food intake (Ong P, et al. 2008).
  - Pruritis may be noted after ingestion of food, which makes the patient scratch and may trigger AD.
  - Late reactions may occur as 6 to 8 hours after food ingestion (Ong P, et al. 2008).
- Serum IgE measurement – Even though a larger number of AD patients have elevated serum IgE levels, approximately 30% have normal levels and do not present with allergic sensitization to allergens (Ong P, et al. 2008).
- Skin biopsy – This is not necessary for diagnosis, however it may be essential for excluding other differentials of AD (see Table 3).

Major Features	Minor Features
Pruritis	Xerosis
Typical morphology and distribution	Cutaneous infections
Flexural lichenification of linearity in adults	Early age of onset
Chronic or relapsing dermatitis	Ichthyosis, palmar hyperlinearity and keratosis pilaris
Facial or extensor involvement in infants and children	Nonspecific dermatitis of the hands or feet
Personal or family history of atopy (asthma, atopic dermatitis, contact urticaria)	Raised serum immunoglobulin (Ig) E levels
	Nipple eczema
	Pityriasis alba
	White dermatographism and delayed blanch response
	Anterior subcapsular cataracts
	Perifollicular accentuation
	Course influenced by environmental/emotional factors
	Facial erythema or pallor
	Dennie-Morgan infraorbital folds, orbital darkening

\*\*At least 3 major and minor features must be present for a diagnosis of atopic dermatitis.

Table 1. Hanifin-Rajka Diagnostic Criteria for Atopic Dermatitis (Ghazvini, et al. 2010)

<b>Essential Features</b> (must be present)	Pruritis Eczema (with typical morphology for age) Chronic or relapsing history
<b>Important Features</b> (seen in most cases; add support to diagnosis)	Early age at onset Personal or family history of atopy or IgE reactivity Xerosis Cutaneous infections Nonspecific dermatitis of the hands or feet Elevated serum IgE levels Positive skin test for immediate-type allergy
<b>Associated Features</b> (nonspecific; help suggest diagnosis)	Atypical vascular response (facial pallor, white dermatographism) Keratosis pilaris, hyperlinearity of palms Pityriasis alba Nipple eczema Ocular or periorbital changes, including anterior subcapsular cataracts, Dennie-Morgan infraorbital folds, orbital darkening Perioral or periauricular lesions Perifollicular accentuation, lichenification or prurigo lesions

Table 2. Diagnostic Criteria for Atopic Dermatitis by the American Academy of Dermatology (Ong P, et al. 2008)

Other dermatosis <ul style="list-style-type: none"><li>- Contact dermatitis</li><li>- Irritant dermatitis</li><li>- Nummular dermatitis</li><li>- Seborrheic dermatitis</li><li>- Psoriasis ichthyosis</li></ul>	Immunodeficiency syndromes <ul style="list-style-type: none"><li>- Wiskott-Aldrich syndrome</li><li>- Severe combined immunodeficiency syndrome with Omen’s</li><li>- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked</li><li>- Graft vs host disease</li><li>- Dermatitis herpetiformis</li></ul>
Infections <ul style="list-style-type: none"><li>- Dermatophytosis</li><li>- Scabies</li></ul>	Metabolic and nutritional deficiencies <ul style="list-style-type: none"><li>- Phenylketonuria</li><li>- Zinc deficiency</li><li>- Niacin deficiency</li><li>- Pyridoxine deficiency</li></ul>
Malignancies <ul style="list-style-type: none"><li>- T cell lymphoma/mycosis fungoides</li><li>- Letterer-Siwe disease</li></ul>	

Table 3. Differential Diagnosis in Atopic Dermatitis (Deshazo, 2009)7. Treatment



## **7. Treatment**

### **7.1 Nonpharmacological interventions**

#### **7.1.1 Dietary restrictions**

Hen's egg, milk, wheat, soy, peanuts, nuts, and fish are responsible for 90% of the food allergy in patients with atopic dermatitis (Sircherer & Sampson, 1999). Avoiding these foods, and other foods suspected to cause flares may be helpful in reducing disease exacerbation, especially in children. Several studies identified the effects of dietary restriction in children with atopic dermatitis. One of these trials, conducted by Sloper and associates evaluated 78 children with atopic dermatitis. Patients were on a diet, which excluded cow's milk, eggs, and foods known to trigger exacerbations. At the end of the trial, 64 patients experienced an improvement in their atopic dermatitis symptoms (Sloper, et al. 1991). Few studies in this meta-analysis used validated diagnostic criteria, which could have given skewed results. Because there are no precise findings in these studies, foods containing milk, eggs, or other known causes of disease flares should be avoided in patients with atopic dermatitis.

#### **7.1.2 Aeroallergen reduction**

Like with food allergens, different aeroallergens such as dust mites, pollen, mold, and animal dander can cause AD exacerbation. This exacerbation can be triggered either by inhalation or direct contact. Fungus and cockroaches have also been suspected (Michel, et al. 2009; Simon-Nobbe, et al. 2008). There have been conflicting studies that show avoidance of aeroallergens, particularly dust mites, reduce disease symptoms. A double-blind, placebo controlled study using dust mite reducing measures in the home proved to improve the symptoms of atopic dermatitis (Tan, et al. 1996). By contrast, there are also trials that show the reduction in aeroallergens have no affect on symptoms of atopic dermatitis (Koopman, et al. 2001; Oosting, et al. 2002). Although the data varies, there is no harm in taking dust mite reducing measures. Aeroallergen reduction techniques that can be used include: using dust mite-proof encasings on pillows, mattresses, and box springs, washing bedding in hot water weekly, removal of bedroom carpet, and decreasing indoor humidity levels with air conditioning (Arlian & Platts-Mills, 2001).

#### **7.1.3 Detergent and chemical avoidance**

Because there is a higher chance of skin irritation in patients with atopic dermatitis, it is important to avoid those products or chemicals that can cause disease exacerbation (Nassif, et al. 1994). Certain soaps, fabric softeners, perfumes, cosmetics, and lotions contain alcohol and other ingredients that can be irritating to the skin of those patients with AD. These products can induce the itch-scratch cycle and worsen symptoms. It is suggested that laundry detergents containing enzymes can also worsen symptoms. A blinded crossover trial of 25 adults looked at the affect on atopic dermatitis symptoms with enzyme-enriched detergent, and a control detergent, which contained no enzymes. Although no diagnostic criteria were described in the trial, the SCORAD index was used to evaluate the patients' severity of symptoms. There was no statistical difference in symptomatic relief between the two groups of patients (Andersen, et al. 1998). However, enzyme-enriched products should be avoided in patients with known hypersensitivity to enzyme proteins.

#### 7.1.4 Phototherapy

The use of natural sunlight for the treatment of atopic dermatitis has been shown to be beneficial, but sunburn should be avoided. If sunlight occurs in the presence of high humidity, or heat which triggers sweating, aggravation of symptoms can occur. Ultraviolet (UV) light (UVB, narrowband UVB, and high-intensity UVA) therapy can be useful in adjunct with other treatments options for patients. Topical glucocorticoid therapy, high-dose UVA1 phototherapy, and UVA-UVB phototherapy were compared in patients with atopic dermatitis. This was a randomized, multi-center trial that found significant differences in favor of high-dose UVA1 and fluocortolone therapy were observed ( $p < 0.0001$ ), as compared with UVA-UVB therapy. At day 10, high-dose UVA1R was superior to fluocortolone ( $p < 0.002$ ) therapy. (Krutmann, et al. 1998). There are also several small trials that look at specific wavelengths of and equipment for UV therapy. Chemophototherapy, psoralen with UVA (PUVA), has also been shown to be effective, but should be limited to those patients with widespread AD. Comparison studies with PUVA are limited. Short-term adverse events of UV phototherapy are mild and include: erythema, pruritis, and pigmentation. Potential long-term adverse effects include: premature skin aging, and cutaneous malignancies (Leung, et al. 2004). UV phototherapy is proven to be an effective method of therapy, because of this it is usually used as a second or third line of treatment.

#### 7.1.5 Psychological approaches

Patients with atopic dermatitis are shown to have significant issues with anxiety, anger, and emotional stress (Bender 2002). They usually respond to embarrassment, frustration, anxiety, or other upsetting events with increased pruritis and scratching (Kodama, et al. 1999). Although emotional factors do not cause atopic dermatitis, studies show that psychological techniques, such as stress reduction approaches, behavior modifications, and group counseling sessions may reduce the exacerbation of atopic dermatitis, particularly those prone to habitual scratching (Melin, et al. 1986).

### 7.2 Pharmacological therapies

#### 7.2.1 Nonprescription therapies

##### 7.2.1.1 Antihistamines

Oral antihistamines are usually recommended for pruritis. However, a recent study of 16 trials showed no little evidence associated with the relief of pruritis with sedating or non-sedating antihistamines (Klein & Clark, 1999). These observations, however, do not exclude the possibility that individual patients may benefit from antihistamines. Because pruritis can be worse at night, oral histamines have been beneficial at bedtime for their sedative properties in patients experiencing symptoms, and can be used as a short-term adjuvant to topical therapy (Kristal & Klein, 2000). The first generation antihistamines, hydroxyzine, diphenhydramine, and cyproheptadine all have sedative effects, but it is shown hydroxyzine to be more effective than the latter (Denman, 1986; Leung, et al. 1998). Newer generation antihistamines ceterizine, loratadine, and fexofenadine may not be beneficial since they lack the sedating properties of the first generation antihistamines. Topical antihistamines should be avoided to the risk of irritating the skin further (Shelley, et al.



1996). Common side effects of antihistamines include: sedation, dry mouth, constipation, blurred vision, and dizziness.

#### 7.2.1.2 Coal tar preparations

Coal tar has been used to treat skin disorders for centuries. Although the exact pharmacologic effects are unknown, it is thought coal tar has antibacterial, antifungal, antipruritic, and keratoplastic effects (Andrew & Moses, 1999; Grupper, 1971; Lavker, et al. 1981). There is a theoretical risk that coal tar being a carcinogen based on observational studies of workers who use tar components in their occupation, however there have been no increase in cancer with clinical use (Callen, et al. 2007). Coal tar preparations have many disadvantages. Their odor, dark staining color, and side effects make them less desirable to patients. Coal tar comes in a variety of formulations, including creams, gels, shampoos, lotions and soaps. Newer formulations make the preparations more tolerable than older versions (Niordson & Stahl, 1985). It is suggested that coal tar be applied at night to avoid the odor and staining of daytime clothing. Adverse effects associated with coal tar preparations include burning, stinging, folliculitis, and photosensitization (Kristal & Klein, 2000).

#### 7.2.1.3 Emollients

Xerosis contributes to microfissures and cracks which can introduce microbes and allergens under the skin. This usually becomes exacerbated in the cold, dry winter months. Because AD is characterized by a decrease in skin barrier function, moisturizing and skin protection play an important role in the disease. Emollients have long been used for this. Although emollients have not been found to improve atopic dermatitis directly, they are a vital source of skin hydration and protection for these patients. The moisturizing aids are available in the forms of lotions, creams, and ointments, and are usually used in conjunction with corticosteroids. Formulations that contain certain dyes, alcohols, or fragrances can exacerbate atopic dermatitis and should be avoided. Because lotions are less viscous than the other formulations, they contain more water, which can cause an evaporative effect causing further skin drying. Ointments may interfere with appropriate sweat removal and result in sweat retention dermatitis. Emollients are better at maintaining skin hydration when applied after the patient soaks in a lukewarm bath.

### 7.2.2 Prescription therapies

#### 7.2.2.1 Topical preparations

##### 7.2.2.1.1 Topical corticosteroids

Topical corticosteroids have been a standard for treatment of atopic dermatitis and other skin disorders for years. Clinicians who are not familiar with topical corticosteroids can be challenged when providing care, due to the various strengths and formulations in which these medications are available. The decision to use a more or less potent corticosteroids depends on the severity of the dermatitis, location of the lesions, and the type of skin involved. Based on their vasoconstrictor assays, there are six potencies of topical corticosteroids that are available through prescription, please refer to Table 4. Potency of topical corticosteroids depends on the concentration of the medication, but also the delivery vehicle. For example, betamethasone valerate ointment is considered more potent than a foam or cream containing the same medication. In general, the lowest potency that will control symptoms should be used. Low potency corticosteroids are recommended for the

Group 1: Super-High Potency	Vehicle
Betamethasone dipropionate augmented 0.05%	Gel, lotion, ointment
Clobetasol propionate 0.05%	Cream, gel, foam, ointment, solution
Fluocinonide 0.1%	Cream
Halobetasol propionate 0.05%	Cream, ointment
Group 2: High Potency	Vehicle
Amcinonide 0.1%	Ointment
Betamethasone dipropionate 0.05% augmented	Cream
Betamethasone dipropionate 0.05%	Ointment
Desoximetasone 0.25%	Cream, gel, ointment
Desoximetasone 0.05%	Gel
Diflorasone diacetate 0.05%	Ointment
Fluocinonide 0.05%	Cream, gel, ointment, solution
Halcinonide 0.1%	Cream, ointment
Mometasone furoate 0.1%	Ointment
Triamcinolone acetonide 0.5%	Ointment
Group 3: Medium-High Potency	Vehicle
Amcinonide 0.1%	Cream, lotion
Betamethasone dipropionate 0.05%	Cream
Betamethasone valerate 0.1%	Ointment
Desoximetasone 0.05%	Cream
Diflorasone diacetate 0.05%	Cream
Fluocinonide emollient 0.05%	Cream
Fluticasone propionate 0.005%	Ointment
Triamcinolone acetonide 0.1%	Ointment
Triamcinolone acetonide 0.5%	Cream
Group 4: Medium Potency	Vehicle
Betamethasone valerate 0.12%	Foam
Fluocinolone acetonide 0.025%	Ointment
Hydrocortisone valerate 0.2%	Ointment
Mometasone furoate 0.1%	Cream, lotion
Triamcinolone acetonide 0.1%	Cream
Group 5: Medium-Low Potency	Vehicle
Betamethasone dipropionate 0.05%	Lotion
Betamethasone valerate 0.1%	Cream
Desonide 0.05%	Ointment
Fluocinolone acetonide 0.025%	Cream
Flurandrenolide 0.05%	Lotion
Fluticasone propionate 0.05%	Cream
Group 6: Low Potency	Vehicle
Alclometasone Desonate 0.05%	Cream, ointment
Fluocinolone acetonide 0.01%	Oil, cream,
Desonide 0.01%, 0.05%	Cream, gel, foam, lotion

Table 4. Topical Steroids Preparations

face, eyelids, genitalia, and sensitive areas, as well as on young children and infants (Leung & Barber, 2003). More potent corticosteroids are used on other areas of the body in adults and children over 12 years of age.

The dosing application of topical corticosteroids is important in the management of the disease, but there are limited trials on the optimal dose. Potent topical corticosteroids should be used for the shortest duration of time and an emollient used in combination during flare-ups to prevent steroid-related side effects (Akdis, et al. 2006). Corticosteroids should be applied once to twice a day; frequent use does not improve efficacy and increases the risk of side effects (Bleehen, et al 1995; Leung & Barber, 2003). The risk of adverse reactions depends on the drug potency, skin integrity, and length of treatment (Fleischer, 1999). It is the clinician's responsibility to balance the need for a potent corticosteroid with the potential for adverse reactions. Adverse effects of topical corticosteroids can be local or systemic. The latter, which occurs rarely, include adrenal suppression, Cushing's syndrome, cataracts, and glaucoma (Correale, et al. 1999; Ruiz-Maldonado, et al. 1982; Stoppoloni, et al. 1983). Local adverse reactions include skin atrophy, contact dermatitis related to the vehicle, depigmentation, rosacea, steroid acne, and folliculitis (Correale, et al. 1999; Fleischer, 1999; Raimer, 2000). Treatment with topical corticosteroids can also reduce the colonization of *S. Aureas*, which may trigger exacerbations (Lipozencic & Wolf, 2007).

#### 7.2.2.1.2 Topical calcineurin inhibitors

Pimecrolimus and tacrolimus are topical immunosuppressants that selectively inhibit the activation of T cells by inhibiting calcineurin, an enzyme required for the transcription of certain genes that code for specific inflammatory cytokines (Bornhovd, et al. 2002; Grassberger, et al. 2009). These are not recommended as first-line therapy or for mild atopic dermatitis. Pimecrolimus cream 1% and Tacrolimus ointment 0.03% are recommended for second-line therapy for mild to moderate AD in non-immunocompromised patients over two years old who have not been successful with other topical treatments.

Short-term (up to four years) treatment with Tacrolimus has been shown safe and effective in children older than two years of age. In a 12-week randomized, vehicle-controlled, double blind, multicenter study of 351 children, 2 to 15 years of age, with moderate to severe atopic dermatitis, tacrolimus ointment (0.03% and 0.1% concentrations) was safe and significantly more efficacious than the vehicle (Paller, et al. 2001). Studies also show that the calcineurin inhibitors are more effective than topical corticosteroids. In a multicenter, randomized, double-blind, parallel-group comparison of tacrolimus ointment 0.03% and 0.1% with hydrocortisone acetate ointment 1% involved 560 children 2 to 15 years of age (Reitamo, et al. 2002). Both concentrations of tacrolimus were significantly more effective than hydrocortisone acetate.

Pimecrolimus has also shown similar results to tacrolimus. Two identically designed, multicenter, randomized, controlled trials compared pimecrolimus cream 1% with vehicle in 403 children 2 to 17 years of age. Both groups received treatment twice daily for 6 weeks. Results showed significant alleviation of symptoms and signs with pimecrolimus compared with the vehicle (Van Leent, et al. 1998.)

Adverse effects of these two agents are similar. The most common adverse reactions are mild to moderate transient burning, stinging, itching, and erythema at the application site, which tends to resolve after the first few days of treatment (Bekersky, et al. 2001; Kang, et al. 2001; Paller, et al. 2001; Reitamo, et al. 2002; Soter, et al. 2001). They are, however, contraindicated in pregnant or breast feeding women. These agents have been studied for

short term use (two years for pimecrolimus and 4 years for tacrolimus) and have been shown to have favorable outcomes, but have been advised that they be used in accordance to their guidelines due to the potential cancer risk. Long term studies for these drugs are still needed.

#### **7.2.2.2 Systemic immunosuppressants**

There are those individuals in which topical steroid use does not result in complete remission. As result, systemic immunosuppressant along with novel therapeutic options are warranted for severe refractory cases to provide increase in therapeutic options with effective remission rates and limited adverse effects. These subsets of patients should be referred to a specialist (i.e., dermatologist or allergist) for further evaluation. Severe atopic dermatitis may be described as the presence of widespread skin lesions or physically and/or emotionally disabling disease that significantly compromises a patient's quality of life. The following will describe available systemic therapies for atopic dermatitis.

##### *7.2.2.2.1 Corticosteroids*

Systemic corticosteroids are not recommended for chronic or maintenance treatment of atopic dermatitis due to many common side effects associated with their use and possible rebound flaring upon discontinuation (Akdis et al, 2006). Typical side effects include; osteoporosis, cataracts, growth suppression, and poor wound healing. A short course of systemic corticosteroids with taper is recommended to abort an acute flare-up. Recommended dosing with prednisone is 40 to 60 mg daily for three to four days followed by 20 to 30 mg daily for three to four days can be beneficial.

##### *7.2.2.2.2 Cyclosporine*

Cyclosporine has proven beneficial in attenuating exacerbations in adults and children with severe atopic dermatitis. It also may be used for intermittent chronic not just short-term therapy. Cyclosporine is classified as a calcineurin inhibitor, which blocks T cell activation. A dose of 5mg/kg/day divided every 12 hours has been evaluated. Monitoring of trough levels, renal, and hepatic function is essential. A taper by 1mg/kg/day every one to three months is recommended. (Sowden et al, 1991; Brazelli et al, 2002). Common side effects associated with cyclosporine include increased risk of infection, malignancy, nephrotoxicity, hypertension, and seizures.

##### *7.2.2.2.3 Interferons*

Interferon-gamma (IFN-gamma) works by suppressing T helper cell activity along with other immunomodulatory effects (Schmitt 2007). Interferon-gamma (IFN-gamma) has shown varying results in the treatment of severe atopic dermatitis although a couple of trials have shown a reduction in symptoms and body surface involvement (Hanifin et al 1993). Side effects that may occur include granulocytopenia, fever/chills, myalgias, headache, and inject site pain.

Several biological therapies have been studied for severe atopic dermatitis and only a few have shown benefit in small subset of patients. Further studies are necessary before any of these medications can be routinely recommended. Some of the biological therapies that have been evaluated are Omalizumab, Rituximab, Infliximab, Etanercept, Alefacept, and Mepolizumab (Graves et al 2007).

##### *7.2.2.2.4 Antimetabolites, azathioprine, and methotrexate*

Antimetabolites azathioprine and methotrexate have shown usefulness in severe atopic dermatitis. Azathioprine is an antagonist of purine metabolism that inhibits T cell

proliferation. Methotrexate is a folic acid antagonist that inhibits reactions and promotes release of adenosine. It also inhibits lymphocyte proliferation. Adverse effects associated with azathioprine and methotrexate are myelosuppression, hepatotoxicity, gastrointestinal disturbances, and increased risk of infection. Monitoring of hematologic and liver function tests is mandatory (Hon et al 2009; Weatherhead et al 2007).

### **7.3 Emerging therapies**

As discussed, atopic dermatitis is an important skin disorder that leads to significant costs and morbidity to patients, families, and society. Effective therapeutic agents are limited in number, and all have side effects that impede successful long-term use. Consequently, there is a high medical need for better therapies. Bimosiamose, nanocrystalline silver cream, phosphodiesterase-4 inhibitors, and IL-4/IL-3 receptor blockers are considered here.

#### **7.3.1 Bimosiamose**

Bimosiamose is a selectin antagonist that blocks the initial slowing of leukocyte traffic, preventing leukocytes from migrating into the tissue, and may alter cell activation and cell-cell signalling pathways. Currently Bimosiamose is in Phase II clinical testing for asthma, psoriasis, and atopic dermatitis (Revotar Biopharmaceuticals 2011).

#### **7.3.2 Nanocrystalline silver cream**

Nanocrystalline Silver Cream completed preliminary studies evaluating its use in atopic dermatitis. Silver has proven for decades to be an effective antimicrobial agent. It has been the active ingredient for the treatment of burns and other wounds. It has also demonstrated anti-inflammatory activity in animal studies. Human studies are currently in Phase II trials evaluating nanocrystalline silver cream applied twice daily using placebo, 0.5% or 1% cream (ClinicalTrials.gov 2005).

#### **7.3.3 Phosphodiesterase-4 Inhibitors**

Phosphodiesterases play a key role in degrading cAMP, which is an important process in virtually all the cell types involved in the pathophysiology of allergic and inflammatory diseases including asthma and chronic obstructive pulmonary disease (COPD), but also skin diseases such as psoriasis and atopic dermatitis. PDE-4 is the major and most abundant in almost all inflammatory and immune cells. PDE-4 suppresses several pro-inflammatory mechanisms like cytokine generation and secretion, IgE production, proliferation, and histamine generation just to name a few. Topical and systemic therapies are being studied. One general problem is the group associated side effect profile with nausea, emesis, and enhanced gastric acid production being the most critical commonly occurring with systemic therapies. Some examples are topical Atizoram and orally Arofylline. The newly FDA approved Roflumilast (Darilesp®) for severe COPD is being investigated for its utility in atopic dermatitis (Baumer et al 2007).

#### **7.3.4 Interleukin receptor blockers**

Elevated IgE responses and eosinophilia is observed in many patients with atopic dermatitis. This is thought to reflect the increased expression of Th2 cytokines, in particular IL-4, IL-5, and IL-13. Cutaneous infiltration of activated T-cells and their release of cytokines are thought to be key events in the development of atopic dermatitis. There are three ways



of inhibition of IL-4; synthesis inhibitors, binding site inhibitors, and inhibiting intracellular signal transduction. Suplatast tosylate is an example of a synthesis inhibitor developed in Japan and may prove useful for steroid resistant asthma, but data about possible effects in atopic dermatitis are lacking. There are several compounds being studied as therapeutic agents inhibiting the binding site and signal transduction (Hennekes & Asadullah 2002).

## 8. Complications

If AD is not appropriately treated there can be several complications that can arise. It is shown that patients with atopic dermatitis are more susceptible to microorganisms, particularly *S. aureus*. Untreated lesions can result in bacterial infections, and acute inflammatory responses of the skin. Patients with atopic dermatitis can also present with eyelid dermatitis, nipple dermatitis, and cheilitis of the lips. Eyelid dermatitis and chronic blepharitis can result in visual impairment from corneal scarring. Other ocular complications include atopic keratoconjunctivitis, vernal conjunctivitis, and keratoconus (Leung, et al. 2003). Management of AD is important in the prevention of other conditions.

## 9. Role of a clinician

Patient education, in addition to treatment, is a factor that can drastically help improve the health of any patient. The healthcare practitioner plays a very important role in a patients' improvement of atopic dermatitis. They can assist a patient in determining what the causative agent is, and provide counselling on how to avoid that particular agent. A physician's knowledge on appropriate diagnosis and the available treatment options is very important in ensuring optimal care. As the drug experts, pharmacists are also responsible for the care of the patient. By providing practical advice concerning the appropriate use of drug products, such as topical corticosteroids and calcineurin inhibitors, compliance can be optimized and adverse effects minimized. In addition, the pharmacist can diminish the stress and anxiety often experienced by patients and caregivers, particularly parents of infants and children with atopic dermatitis. In addition, a pharmacist can advise undiagnosed or untreated patients' on when it is necessary to receive treatment from a physician.

## 10. Conclusion

Atopic dermatitis is a condition that has no cure, but the main goal of treatment is to reduce disease flares and improve the patients' quality of life. Avoidance of triggering factors, optimal skin care, and pharmacotherapy can produce control of exacerbations in patients. Although there is no cure, there are many safe and effective treatment options available. Corticosteroids remains the standard for therapy, but those unresponsive to corticosteroids have other options including systemic and topical immunomodulators, and non-prescription agents.

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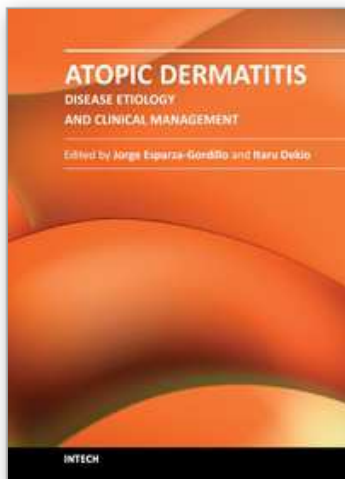
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## **Atopic Dermatitis - Disease Etiology and Clinical Management**

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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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